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The Synthesis of 7-Carbonyl Homologues of 1-Deoxynojirimycin

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Abstract: A 3,4;5,6-di-*O*-isopropylidene salt derivative of 1-amino-1-deoxy-D-glucitol was transformed to *N*-Boc protected (5,6)-α,β-unsaturated 7-carbonyl compounds. Conversion to the title piperidine products proceeded *via* deprotection and intramolecular 1,4-addition of the amino group.

Inhibition of glycosidases may be useful for treatment of several diseases e.g. diabetes,[1] cancer,[2] and some viral infections.[3] Important examples are the antiviral (including anti-HIV) and antidiabetic activities[4] found for the glucosidase inhibitors 1-deoxynojirimycin[5] **1** and castanospermine[6] **2** (Figure 1). The potential chemotherapeutic applications of these natural polyhydroxylated alkaloids and their analogues have prompted considerable synthetic interest towards structural modification, such as the introduction of lipophilic (e.g. fluoro,[7] alkyl,[8] and acyl[9]), amino,[10,11] and glucosyl[12] groups at specific positions of compound **1**. Complete removal of the C-6 hydroxymethyl group of **1** has remarkably little effect on enzyme-substrate interactions.[13]

This report deals with the conversion of 1-amino-1-deoxy-D-glucitol **3** to the trihydroxypiperidines **4-7**. These compounds represent a new class of 1-deoxynojirimycin analogues where the C-6 hydroxyl has been replaced with a ketone, acid or amide carbonyl function.

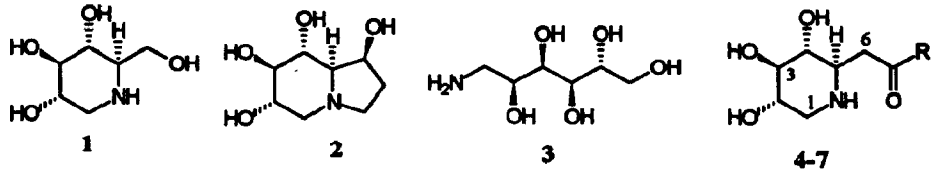
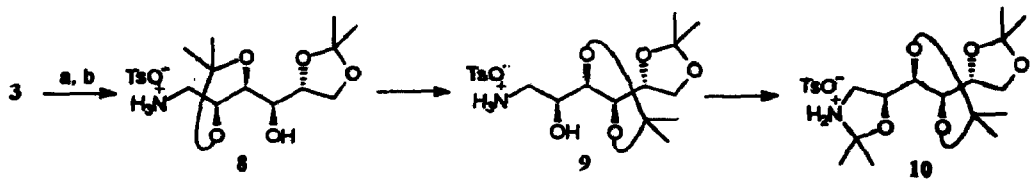


Figure 1

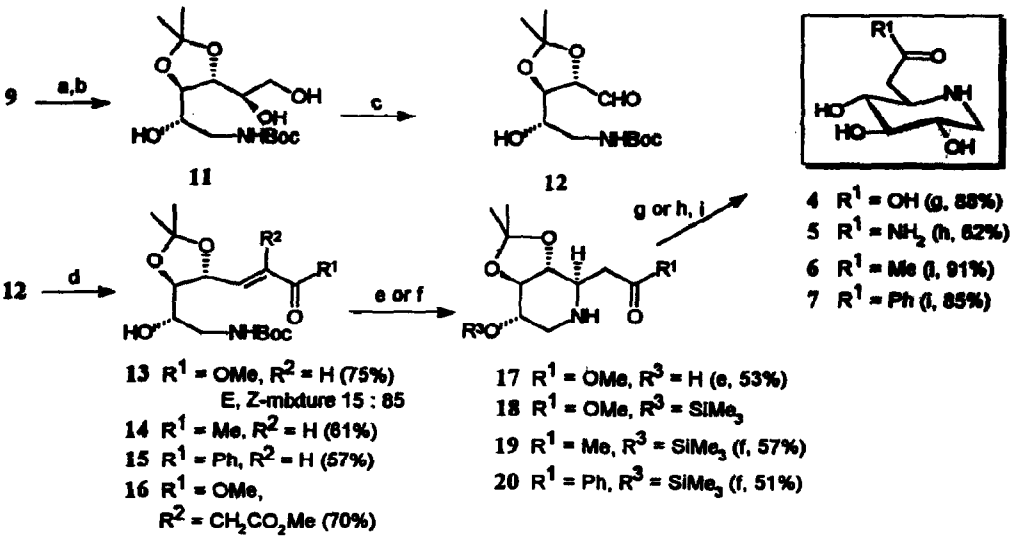
The synthesis started with the preparation of the 3,4;5,6-di-*O*-isopropylidene protected salt **9**. The course of the reaction depicted in Scheme 1 was revealed by t.l.c analysis of the *N*-acylvinyl [$RNHCH{=}C(CO_2Et)_2$] and *N*-Boc derivatives.[14] Under the acidic conditions, the initially formed diacetonide **8** rearranged to the regioisomer **9** which crystallized from the reaction medium. After 24 hours, pure compound **9** was collected by filtration (65% yield), whereas in the filtrate only diacetonide **9** and triacetonide **10** were detected.

Scheme 1.



Experimental conditions:. (a) MeOH, *p*-TsOH.H_2O (1 eq), evaporate to dryness; (b) Me_2CO-$Me_2C(OMe)_2$ (1:3), *p*-TsOH.H_2O (0.5 eq), r.t. 24 h, 65% **9**.

Scheme 2



13 R^1 = OMe, R^2 = H (75%)
E, Z-mixture 15 : 85
14 R^1 = Me, R^2 = H (61%)
15 R^1 = Ph, R^2 = H (57%)
16 R^1 = OMe,
R^2 = CH_2CO_2Me (70%)

17 R^1 = OMe, R^3 = H (e, 53%)
18 R^1 = OMe, R^3 = $SiMe_3$
19 R^1 = Me, R^3 = $SiMe_3$ (f, 57%)
20 R^1 = Ph, R^3 = $SiMe_3$ (f, 51%)

4 R^1 = OH (g, 88%)
5 R^1 = NH_2 (h, 62%)
6 R^1 = Me (i, 91%)
7 R^1 = Ph (i, 85%)

Experimental conditions: (a) PPTS (1 eq), MeOH-H_2O (9:1), 60 °C, 1 h; (b) Na_2CO_3, (*t*-BuOCO)$_2O$, 0.5 h; (c) $NaIO_4$ (1.1 eq), H_2O; (d) R^1COCR^2=PPh_3, (1.2 eq), MeOH or CH_2Cl_2, 0.5 h; silica column (EtOAc-hexane 1:1); (e) Me_3SiI, CH_2Cl_2, r.t., 10 min; MeOH-Et_3N; MeOH-K_2CO_3; silica column (EtOAc-MeOH 94:6); (f) Me_3SiI, CH_2Cl_2, r.t., 5 min; Et_3N; silica column (EtOAc-hexane 3:2); (g) 6M HCl; Dowex 50W-X8 (0.2M NH_4OH); (h) HCl-MeOH; NH_3-MeOH, NaCN, reflux; Dowex 50W-X8 (0.2M NH_4OH); (i) 6M HCl; silica column ($CHCl_3$-MeOH-H_2O-NH_4OH 70:28:1:1).

Diacetonide **9** was converted (Scheme 2) to the crystalline *N*-Boc protected 2,5,6-triol **11** in 81% yield.[15] Selective removal of the 5,6-*O*-isopropylidene group was achieved by heating **9** with pyridinium *p*-toluenesulfonate (PPTS) in aqueous methanol at 60°C. After reaction with (*t*-BuOCO)$_2O$, triol **11** was separated from the *N*-Boc derivative of the remaining diacetonide **9** by successive extraction with toluene and ethyl acetate. The oxidative cleavage of the 5,6-diol group of triol **11** with $NaIO_4$ afforded the unstable L-xylose derivative **12**, which was directly subjected to various Wittig reactions in methanol or dichloromethane. By using the appropriate triphenylphosphoranylidene reagents,[16] the α,β-unsaturated carbonyl compounds **13-16** were isolated in 57-75% yield based on the triol precursor **11**.[17]

Our synthetic plan (Scheme 2) required deprotection of the *N*-Boc amino group and cyclization *via* 1,4-addition to the α,β-unsaturated carbonyl function. Treatment of the ester compound **13** with formic acid for 10 minutes and neutralisation with aqueous Na_2CO_3 gave the desired piperidine compound **17** in only 35% yield. The low yield was due to incomplete deprotection of the amino group and, presumably, to partial cleavage of the isopropylidene group resulting in detection of unidentified polar side products. A more selective deprotection was accomplished by reaction with Me_3SiI in dichloromethane and quenching with methanol and Et_3N. Under these conditions, a mixture of the cyclic compound **18** and the desilylated product **17** was isolated. No cyclization was observed in the absence of methanol. Complete removal of the trimethylsilyl group with K_2CO_3 in methanol produced **17** in 53% overall yield from **13**.

In the analogous conversion of ketones **14** and **15** with Me_3SiI, cyclization of the intermediate primary amines already occurred upon addition of only Et_3N to the reaction mixture. However, for diester compound **16** none of the expected monocyclic and/or bicyclic product was observed on removal of the *N*-Boc group and heating of the resulting primary amine in methanol or 2-butanol.

Conversion of compounds **17-20** to the target compounds **4-7** proceeded *via* acidic cleavage of the protecting groups. Treatment of ester **17** with aqueous 6M HCl for 48 hours followed by ion exchange chromatography provided the crystalline amino acid **4**. The amide **5** was prepared from **17** by sequential removal of the acetal group with methanolic HCl and ammonolysis of the resulting ester intermediate. The ammonolysis was effected by prolonged heating with methanolic ammonia using NaCN as a catalyst.[18] After acidic deprotection of **19** and **20** with 6M HCl, the ketone target compounds **6** and **7** were isolated by column chromatography on silica gel.[17]

Analysis of the ^1H NMR spectra of the *trans*-fused acetonides **17-20** and the deprotected compounds **4-7** revealed the all-equatorial orientation of the substituents, as shown by the coupling constant values $J_{5,4} = J_{4,3} = J_{3,2} = 9$ Hz.[19] Hence, 1,4-addition of the amino group to the α,β-unsaturated carbonyl system proceeds in a diastereospecific way producing the C-6 equatorial isomer exclusively.

The acetonides **17-20** represent advanced intermediates showing the desired variety of protected and non protected functional groups. When further modified and deprotected, they may provide access to a large number of variously substituted analogues, in addition to the C-6 extended homologues **4-7** resulting from simple hydrolysis.

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14. Samples of the reaction mixture were treated with aqueous Na_2CO_3 and diethyl ethoxymethylenemalonate or di-*tert*-butyl dicarbonate. T.l.c. analysis (hexane-EtOAc, 7:3) revealed the *N*-acylvinyl derivatives of **8** and **9** (**8** more polar than **9**) or the corresponding *N*-Boc derivatives (R_F **8** = R_F **9** = 0.2) and the *N*-Boc triacetonide **10** (R_F = 0.5). The secondary amine does not react with the acylvinyl reagent.
15. Crystallized from hexane-EtOAc, mp 93-94 °C, $[\alpha]_D^{18}$ +8,57° (*c* 0.2, MeOH). HRMS for tris-*O*-trimethylsilyl derivative, calcd. for $C_{22}H_{48}NO_7Si_3$ ($[M-CH_3]^+$) 522.2739, found 522.2741. The 81% yield for triol **11** includes material (28%) obtained by subjecting the *N*-Boc diacetonide fraction resulting from non hydrolyzed **9** to the PPTS acid hydrolysis.
16. The reactions were conducted in MeOH except for the use of CH_2Cl_2 in the preparation of **16**. The commercial reagents $RCOCH{=}PPh_3$ (R = OMe, Me) were used. $PhCOCH{=}PPh_3$ was generated *in situ* by treatment of commercial phenacetyltriphenylphosphonium bromide with MeONa. The reagent $MeO_2C\text{-}C(CH_2CO_2Me){=}PPh_3$ was prepared by using a modification of the method reported by Cameron, A. F.; Duncanson; F. D; Freer, A. A.; Armstrong, V. W.; and Ramage, R.; *J. Chem. Soc. Perkin Trans II* **1975**, 1030.
17. Satisfactory spectral data (IR, 400 MHz ^1H NMR, ^{13}C NMR, EI and CI mass spectra) were obtained for all new compounds. HRMS data were acquired for all new compounds (M^+ or significant fragment ions were measured). Compounds **4**, **6**, and **11** were analysed as the trimethylsilyl derivatives.
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19. Selected NMR data :**4** ^1H NMR 400 MHz (D_2O), δ (ppm) 2.11 (dd, J = 9, 16 Hz, 1 H, H-6a), 2.47 (dd, J = 11, 12 Hz, 1 H, H-1*ax*), 2.72 (dd, J = 3, 16 Hz, 1 H, H-6b), 2.73 (m, 1 H, H-5), 3.06 (dd, J = 5, 12 Hz, 1 H, H-1*eq*), 3.08 (t, J = 9 Hz, 1 H, H-4), 3.28 (t, J = 9 Hz, 1 H, H-3), 3.48 (ddd, J = 5, 9,12 Hz, 1 H, H-2); ^{13}C NMR 100 MHz 39.7 (C-6), 48.9 (C-1), 57.5 (C-5), 70.6 (C-2), 74.4 (C-4), 78.3 (C-3), 180.2 (COOH). **5** ^1H NMR 400 MHz (D_2O), δ (ppm) 2.18 (dd, J = 9, 16 Hz, 1 H, H-6a), 2.40 (dd, J = 11, 12 Hz, 1 H, H-1*ax*), 2.71 (dd, J = 3, 16 Hz, 1 H, H-6b), 2.78 (td, J = 3, 9 Hz, 1 H, H-5), 3.02 (dd, J = 5, 12 Hz, 1 H, H-1*eq*), 3.05 (t, J = 9 Hz, 1 H, H-4), 3.25 (t, J = 9 Hz, 1 H, H-3), 3.43 (ddd, J = 5, 9, 12 Hz, 1 H, H-2); ^{13}C NMR 100 MHz 37.3 (C-6), 48.6 (C-1), 56.8 (C-5), 70.5 (C-2), 74.2 (C-4), 77.8 (C-3), 176.6 ($CONH_2$). **6** ^1H NMR 400 MHz (D_2O), δ (ppm) 2.15 (m, 1 H, CHDCO), 2.17 (s, 1 H, CD_2HCO), 2.42 (t, J = 11, 12 Hz, 1 H, H-1*ax*), 2.87 (m, 1 H, H-5), 3.01 (dd, J = 5, 12 Hz, 1 H, H-1*eq*), 3.07 (t, J = 9 Hz, 1 H, H-4), 3.24 (t, J = 9 Hz, 1 H, H-3), 3.44 (ddd, J = 5, 9, 12 Hz, 1 H, H-2); ^{13}C NMR 100 MHz 29.8 CH_3CO), 44.5 (CH_2CO), 48.5 (C-1), 55.7 (C-5), 70.3 (C-2), 73.9 (C-4), 77.8 (C-3), 213.4 (CO). **7** ^1H NMR 400 MHz (CD_3OD), δ (ppm) 2.60 (*br* t, J = 12 Hz, 1 H, H-1*ax*), 3.13 (m, 1 H, H-5), 3.16 (dd, J = 5, 12 Hz, 1H, H-1*eq*), 3.22-3.33 (m, 2 H, H-3, H-4), 3.56 (m, 1 H, H-2); 7.50, 7.62, 8.01 (m, 5 H, Ph); ^{13}C NMR 100 MHz 40.4 (C-6), 50.7 (C-1), 58.0 (C-5), 71.7 (C-2), 75.0 (C-4), 80.1 (C-3), 129.3, 129.8, 134.7, 138.1 (C *arom.*), 201.0 (CO).

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